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General introduction to cancer cytogenetics of mature B-cell lymphomas (follicular lymphoma, diffuse large B-cell lymphoma & Burkitt lymphoma)

The following chapter is a selection of the published book chapter and a full version including other mature B-cell lymphoma entities, Hodgkin lymphoma and T-cell lymphomas has been published in:

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Mature lymphoid neoplasms are an extremely heterogeneous group of malignancies with regard to biological, clinical, and morphological features (Jaffe et al., 2001; Swerdlow et al., 2008). The clinical presentation mainly includes leukemic forms and tumors affecting predominantly lymphatic organs, such as the lymph nodes or spleen, or nonlymphatic organs, such as the skin or central nervous system (CNS). Both solid and circulating phases are not infrequently present together in lymphoid neoplasms rendering distinction between “leukemia” and “lymphoma” artificial in many cases. The natural course run by the different diseases ranges from the rather indolent, like in some types of chronic lymphocytic leukemia (CLL) or follicular lymphoma (FL), to the highly aggressive, as exemplified by Burkitt lymphoma (BL).

Historically, the main division of mature lymphoid neoplasms has been between Hodgkin disease, nowadays called Hodgkin lymphoma (HL), and non-Hodgkin lymphoma (NHL). More than 99% of HL and approximately 85% of mature lymphoid neoplasms generally derive from lymphoid cells of the B-lineage, the remainder being derived from the T/natural killer (NK)-cell lineage. Considering this biological and clinical heterogeneity as well as the relatively easy access to samples from lymphatic malignancies, it is not surprising that a huge number of chromosomal aberrations have been described in mature lymphoid neoplasms and also that many of them are nonrandom or even specific (Mitelman et al., 2014). Since Manolov and Manolova (1972) first described a 14q + marker chromosome in BL and Zech et al. (1976) identified the marker as stemming from a t(8;14)(q24;q32), the first characteristic translocation to be identified in a malignant lymphoma, the karyotypes of several thousand mature lymphoid neoplasms have been made publicly available, and many of the recurrent aberrations have been molecularly characterized. Novel cryptic chromosomal rearrangements are continuously being identified using molecular cytogenetic approaches such as fluorescence *in situ* hybridization (FISH); microarray-based technologies, including array comparative genomic hybridization (aCGH); and lately also highthroughput sequencing (for reviews, see Martin- Subero et al., 2003a, 2003b; Schwaenen et al., 2003; Dewald et al., 2004; Kearney and Horsley, 2005; Ventura et al., 2006; Nieländer et al., 2007; Wolff et al., 2007; Kluin and Schuuring, 2011; Campo, 2013). The new information obtained via a variety of recently introduced techniques is constantly refining our picture of the chromosome aberrations of malignant lymphomas and chronic lymphoproliferative disorders, deepening our understanding of how molecular and chromosomal rearrangements are crucial events

in tumorigenesis. Nevertheless, the new technologies in no way render superfluous the cytogenetic analysis of banded chromosomes in metaphase plates: also, high-throughput sequencing suffers from limitations in, among other things, the ability to detect chromosomal fusions with the breakpoints in repetitive-rich sequences (e.g., Robertsonian translocations or rearrangements involving immunoglobulin loci). The new technological approaches refine our diagnostic abilities rather than supplant the time-honored, older techniques.

Classification of mature lymphoid neoplasms

The identification and characterization of recurrent chromosomal changes in the tumor cells has influenced and continues to have a major impact on the classification of mature lymphoid neoplasms (Harris et al., 1994; Jaffe et al., 2001, Swerdlow et al, 2008; Kluin and Schuuring, 2011). For example, mantle cell lymphoma (MCL) was only accepted as a separate entity once the translocation t(11;14)(q13;q32) leading to cyclin D1 activation through the juxtaposition of *CCND1* to *IGH* was identified as a genetic hallmark of this disease (Banks et al., 1992).

A problem when assessing the many cytogenetic studies providing the data on which this chapter is based is that most of them were performed before the publication and widespread acceptance of the “WHO classification of tumors of hematopoietic and lymphoid tissues” (Jaffe et al., 2001; Swerdlow et al., 2008). Thus, in many instances, the diagnosis then given is no longer considered valid, or it may not even exist anymore; in fact, it is for this very reason that the title of the present chapter has been changed from that of the earliest editions of *Cancer Cytogenetics*. Usually, the new classification reflects an increased understanding of disease biology; for example, what was formerly called t(11;14)-positive CLL or B-cell prolymphocytic leukemia (B-PLL) is today, based on modern immunophenotyping analyses, mostly diagnosed as (leukemic) MCL or “MCL-like” disease (van der Velden et al., 2014), and cases of true t(11;14)-positive CLL or B-PLL are hardly recognized any longer. In addition, the detection of novel cytogenetic correlations and the increased use of new gene expression and sequencing technologies make regular revisions of the WHO classification necessary. The present chapter widely relies on the 2001 and 2008 WHO classifications (Swerdlow et al., 2008). However, as we write, a new update of the WHO classification is already being prepared. We therefore try to comment also on such genetic findings that are likely to be featured there.

The WHO classification groups lymphoid neoplasms according to four main criteria, namely, their clinical, morphologic, immunophenotypic, and genetic features. The relative diagnostic importance of these parameters differs among diseases; there is no one "gold standard" (Jaffe et al., 2001; Swerdlow et al., 2008). For each neoplasm, a cell of origin (COO) is postulated. Often, this putative COO represents the stage of differentiation rather than the cell in which the actual initial transforming event occurred, since the latter is not known with certainty. Therefore, the classification is widely based on how we perceive normal B- and T-cell developments to proceed.

The cytogenetic findings will be presented under the main headings "Mature B-cell neoplasms," "Mature T-cell and NK-cell neoplasms," and "HL." For the convenience of the reader, at the beginning of each section, a tabular comparison of the most important relevant classification systems is provided.

B- and T-cell development and physiological B- and T-cell receptor rearrangements

The development and maturation of B and T lymphocytes are tightly regulated processes that take place in the bone marrow, peripheral blood, and lymphoid organs. Every maturation stage is characterized by physiological genetic rearrangements and expression of certain surface molecules and cytokines (for reviews, see Küppers et al., 1999; Küppers and Dalla-Favera, 2001; Küppers, 2005; Seifert et al., 2013).

The cells of the immune system are able to recognize multiple antigens through a multitude of different antigen-specific receptors. This diversity is generated through programmed intrachromosomal rearrangements of the genes encoding immunoglobulins (*IG*) in B lymphocytes and Tcell receptors (*TCR*) in T lymphocytes. These genes contain all or part of gene segments for variability (*V*), diversity (*D*), joining (*J*), and constant (*C*) sequences. Rearrangements of the *V, D,* and *J* genes are responsible for the great variability and specificity of the immune system.

Immunoglobulin molecules, also called antigen receptors or antibodies, are composed of Ig heavy chains (IgH) and light chains, either kappa (Igκ) or lambda (Igλ). These proteins are encoded by the *IGH* locus at chromosome band 14q32, *IGK* at 2p12, and *IGL* at 22q11. The *IGH* gene is composed of *V, D, J,* and *C* gene segments (Figure 2.1), whereas *IG* light-chain genes lack *D* segments. In

the bone marrow, B-cell development is initiated by rearrangements of *IGH* and *IGK/L* loci in B-cell progenitors. The so-called *V(D)J* in *IGH* (Figure 2.1) and *VJ* in *IGK/L* recombinations create a functional Ig. This Ig, of IgM isotype but also IgD in mature B cells, is expressed on the surface of B cells and is essential for cell development and survival. Those cells that produce nonfunctional rearrangements die by apoptosis. B cells leave the bone marrow to become mature, naive (not exposed to antigen) cells that travel through the bloodstream to secondary lymphoid organs such as the lymph nodes, spleen, and mucosa-associated lymphoid tissue (MALT). There, the B cells that interact with antigens through membrane-bound Ig are clonally selected and undergo a process of proliferation and differentiation to create a germinal center. The genomic DNA is then modified by receptor editing, class switching, and somatic hypermutation.

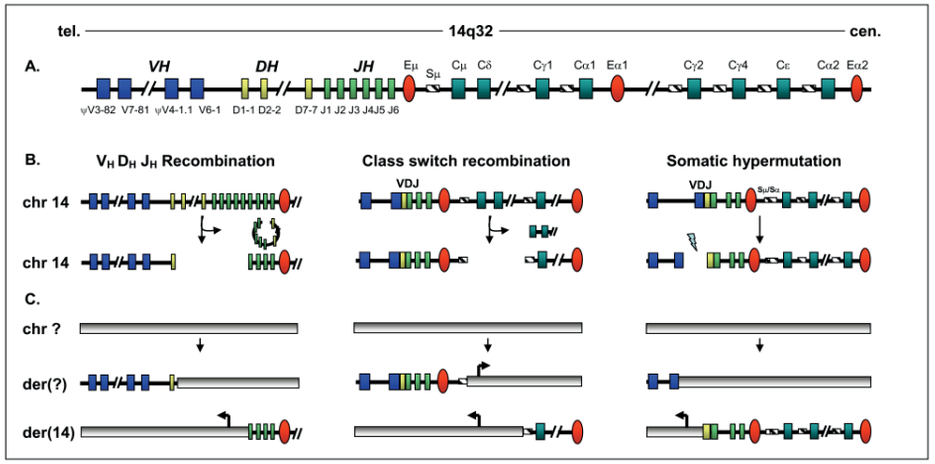

Figure 2.1 | Schematic representation of the mechanisms leading to *IGH* translocations in B-cell malignancies (based on Willis and Dyer, 2000; Küppers and Dalla-Favera, 2001). (A) *IGH* locus germline configuration displaying variable (*V*H), joining (*J*H), diversity (*D*H), and constant (*C*) regions. Switch regions (black and white rectangles) lie upstream of each constant region with the exception of *C*δ. *E*μ and *E*α enhancers are shown in red. (B) Schematic representation of the *VDJ* recombination, class switch recombination, and somatic hypermutation mechanisms. (C) Formation of *IGH* translocations. Depending on the breakpoint location at 14q32, the *IGH* locus may deregulate proto-oncogenes in both partner chromosomes through the translocation (elbowed arrows).

Receptor editing is a process by which an originally expressed antibody polypeptide chain, usually a light chain, is replaced by another one. The process is mediated by secondary rearrangements of the variable region segments. Some B cells change their Ig isotype from IgM and IgD to IgG, IgA, or IgE, a process

called class switching (Figure 2.1). This event is mediated through further recombinations of the *IGH* locus, by which DNA between switch regions immediately upstream of the constant regions is deleted. Somatic hypermutation is the process by which mutations are introduced into the variable sequences of *IG* genes to increase the affinity for the antigen. Eventually, some of these cells with mutant antibodies expressing increased affinity are released to the peripheral blood as antibody-secreting cells, plasma cells, or long-lived memory cells.

The T-cell receptor is a heterodimer composed of either α and β or γ and δ chains. The genes encoding these proteins are *TCRA/D* located at 14q11, *TCRB* at 7q34, and *TCRG* at 7p14. The process by which these genes are assembled to make a functional T-cell receptor is similar to that occurring at *IG* loci in B cells. However, in contrast to B lymphocytes, T lymphocytes proliferate and differentiate along several different developmental pathways generating distinct subpopulations of mature T cells.

Chromosomal translocations involving IG and TCR loci

IG loci, including both the *IGH* locus in 14q32 and the *IGK* and *IGL* light-chain loci in 2p12 and 22q11, respectively, are recurrently involved in many chromosomal translocations in mature Bcell malignancies (Table 2.1). In contrast, the TCR loci are rather seldom involved in structural aberrations in mature T-cell neoplasms with the notable exception of T-cell prolymphocytic leukemia (T-PLL), in which *inv(14)(q11q32)* and its variant *t(14;14)(q11;q32)* are present in approximately 80%, with some of the remaining cases showing the rare but recurrent t(X;14)(q28;q11) (discussed in the following).

The frequency of IG translocations in different subtypes of mature B-cell malignancies is quite variable. For some diseases, like BL with its *t(8;14) (q24;q32)* and light-chain variants or MCL with its *t(11;14)(q13;q32)*, one or a group of distinct IG translocations are pathognomonic for the disease and, hence, detectable in more than 95% of all cases (Fu et al., 2005; Hummel et al., 2006; Jares et al., 2007; Salaverria and Siebert, 2011). In other instances, like diffuse large B-cell lymphoma (DLBCL) or multiple myeloma (MM), IG translocations are detectable in roughly half of the cases but recombining with a large number of partners (Siebert et al., 2001; Kuehl and Bergsagel, 2002; Lenz et al., 2007; Martin et al., 2010; Walker et al., 2013). At the other end of the spectrum, CLL is notable for its lack of IG translocations, and when breaks do occur at 14q32 in this disease, they do not always involve the *IGH* locus (Nowakowski et al., 2005; Wlodarska et al., 2007).

IG translocations in malignant B cells may be multiple and may involve both *IGH* and a light-chain locus. A common combination is that of a *t(14;18)(q32;q21)* in FL being followed by a t(8;14) or a corresponding t(2;8) or t(8;22) variant at transformation to DLBCL (Knezevich et al., 2005; Martin-Subero et al., 2005). Such cases, known as “double-hit” lymphomas if they involve IG translocations to *MYC* and either *BCL2* or *BCL6*, are usually clinically aggressive and respond poorly to chemotherapy (Aukema et al., 2011). The latter example also shows that hardly any of the IG translocations in mature B-cell neoplasms is completely specific for a certain lymphoma subtype. For example, t(11;14) (q13;q32) is recurrent in both MCL and MM and t(14;18)(q32;q21) is recurrent in both FL and DLBCL but also recurrently occurs, in addition to trisomy 12, in CLL. The t(8;14)(q24;q32) and its variants can occur, besides in BL, in almost any kind of mature B-cell neoplasm, including CLL, MCL, FL, and DLBCL (Karsan et al., 1993; Au et al., 1999, 2000, 2002, 2004; Sen et al., 2002; Majid et al., 2007; Aukema et al., 2011, 2014; Horn et al., 2011; Put et al., 2012; de Oliveira et al., 2014).

Chromosomal translocations affecting IG loci that look identical at the cytogenetic level are also often identical in terms of which genes they target. In contrast, sometimes different partner genes are involved in seemingly identical translocations, like *BCL2* and *MALT1*, which recombine with *IGH* in t(14;18)(q32;q21) in FL and MALT lymphoma, respectively (Tsujimoto et al., 1985; Sanchez- Izquierdo et al., 2003; Streubel et al., 2003).

As outlined earlier, all IG loci are subject to multiple physiological breaks as part of recombination events during B-cell development. Chromosomal translocations are supposed to derive from mistakes in these recombination processes. Depending on whether mistakes occur in the V(D)J joining process, during class switching, or as by-products of somatic hypermutation, the chromosomal breakpoints are found in different regions of the IG loci (Figure 2.1). With regard to the heavy-chain locus, class switch-associated translocations affect the centromeric part of *IGH* in 14q32 containing the segments for the constant Ig regions, VDJassociated translocations mostly affect the middle part of *IGH* that contains the J-segments, and somatic hypermutation-associated translocations predominantly affect the telomeric part of the *IGH* locus containing the V-segments (Willis and Dyer, 2000; Küppers and Dalla-Favera, 2001; Kuehl and Bergsagel, 2002; Dyer, 2003; Küppers, 2005).

The location of the IG breakpoint is supposed to reflect the developmental stage at which the translocation occurs in a B cell. In line with this hypothesis, the t(11;14)(q13;q32) of MCL, which is supposed to occur in a pregerminal center cell in the bone marrow through an unsuccessful *VDJ* rearrangement, mostly involves a J-segment. In contrast, the cytogenetically identical translocation in a subset of MM stems from a failed class switch recombination event supposed to take place in or after the germinal center and affects the region containing the constant genes (Walker et al., 2013). Similarly, IG translocations in FL are, with very rare exceptions (Fenton et al., 2002), supposed to derive from mistakes in the *VDJ*-recombination process, whereas those occurring in DLBCL, MM, or CLL mostly involve class switch regions (Willis and Dyer, 2000; Küppers and Dalla-Favera, 2001; Kuehl and Bergsagel, 2002; Dyer, 2003; Küppers, 2005). Remarkably, the t(8;14)(q24;q32) in endemic BL mostly involves the J, whereas the same translocation in sporadic BL mostly affects a constant region, indicating that different pathogenetic mechanisms are at work in the two situations (reviewed in Boxer and Dang, 2001; Küppers and Dalla-Favera, 2001).

The consequences of the IG translocations are activation of intact oncogenes through deregulation mediated by enhancer segments within the IG loci. Only on rare occasions are fusion transcripts of the IG and oncogenes generated (Willis and Dyer, 2000). Although *VDJ*-associated translocations of the *IGH* locus lead to activation of the oncogene on the der(14) through juxtaposition of the translocated oncogene with the *IGH* enhancer, class switch translocations in principle can activate oncogenes on both derivative chromosomes because the centromeric *IGH* enhancer(s) remains on der(14), whereas the telomeric IGH enhancer(s) translocates to the derivative partner chromosome (Figure 2.1). This explains why recurrent loss of the der(11) t(11;14) in MCL or der(14)t(4;14) in MM does not affect deregulation of the *CCND1* and *MMSET* genes in 11q13 and 4p16, respectively (Santra et al., 2003). In translocations affecting the *IGK* and *IGL* light-chain loci, the oncogenic activation usually takes place on the derivative partner chromosomes to which the enhancer elements were translocated (Willis and Dyer, 2000; Küppers and Dalla-Favera, 2001; Kuehl and Bergsagel, 2002; Dyer, 2003; Küppers, 2005; Kroenlein et al., 2012; Shimanuki et al., 2013).

Table 2.1 | Chromosomal translocations and other structural aberrations affecting the *IGH* locus in 14q32, the *IGK* locus in 2p12, or the *IGL* locus in 22q11 in mature B-cell malignancies other than multiple myeloma

Translocation	Lymphoma/leukemia subtype	Partner	References
t(1;14)(p22;q32)*	Mucosa-associated lymphoid tissue (MALT) lymphoma	*BCL10*	Willis et al. (1999) and Zhang et al. (1999)
t(1;14)(q21;32)	Diffuse large B-cell lymphoma	*MUC1*	Dyomin et al. (2000) and Gilles et al. (2000)
t(1;14)(q21;32)	Diffuse large B-cell lymphoma	*IRTA1*	Sonoki et al. (2004)
t(1;14)(q21;32)	Follicular lymphoma	*FCGR2B*	Chen et al. (2001a)
t(1;22)(q21;q11)	Follicular lymphoma	*FCGR2B*	Callanan et al. (2000)
t(2;7)(p11;q21)	Indolent B-cell lymphoproliferative disorders, splenic marginal zone lymphoma	*CDK6*	Corcoran et al. (1999) and Parker et al. (2011, 2013)
t(2;14)(p13;q32)	B-CLL, immunocytoma	*BCL11A*	Satterwhite et al. (2001)
t(3;14)(p14;q32)	MALT lymphoma, diffuse large B-cell lymphoma	*FOXP1*	Streubel et al. (2005)
t(3;14)(q27;q32)*	Diffuse large B-cell lymphoma, follicular lymphoma	*BCL6*	Kerckaert et al. (1993) and Ye et al. (1993a)
t(4;14)(q24;q32)	Posttransplant lymphoproliferative disorder	*BANK1*	Yan et al. (2014)
t(6;14)(p21;q32)*	Diffuse large B-cell lymphoma, other B-cell lymphomas	*CCND3*	Sonoki et al. (2001)
t(6;14)(p25;q32)	(Pediatric) diffuse large B-cell lymphoma/FL3B	*IRF4*	Salaverria et al. (2011)
t(6;14)(q15;q32)	Aggressive B-cell lymphoma, NOS	*BACH2*	Kobayashi et al. (2011)
t(7;14)(q21;q32)*	Splenic lymphoma with villous lymphocytes	*CDK6*	Corcoran et al. (1999)
t(8;14)(q24;q32)*	Burkitt lymphoma/leukemia, diffuse large B-cell lymphoma, B-cell prolymphocytic leukemia, multiple myeloma	*MYC*	Taub et al. (1982)
t(9;14)(p13;q32)	Lymphoplasmacytoid immunocytoma, other B-NHL	*PAX5*	Busslinger et al. (1996) and Iida et al. (1996)
t(9;14)(q33;q32)	Pediatric chronic myeloid leukemia (blast crisis)	*LHX2*	Nadal et al. (2012)
t(10;14)(q24;q32)	Diffuse large B-cell lymphoma	*NFKB2 (LYT10)*	Neri et al. (1991)
t(11;14)(p13;q32)	Diffuse large B-cell lymphoma, follicular lymphoma	*CD44*	Hu et al. (2012)

Translocation	Lymphoma/leukemia subtype	Partner	References
t(11;14)(q13;q32)*	Mantle cell lymphoma, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, splenic lymphoma with villous lymphocytes	*CCND1 (BCL1)*	Motokura et al. (1991) and Rosenberg et al. (1991)
t(11;14)(q23;q32)	Primary mediastinal B-cell lymphoma	*PAFAH1A2*	Lecointe et al. (1999)
t(11;14)(q23;q32)	Diffuse large B-cell lymphoma	*RCK*	Akao et al. (1992)
t(12;14)(p13;q32)*	Mantle cell lymphoma	*CCND2*	Gesk et al. (2006) and Herens et al. (2008)
t(12;14)(q24;q32)	Burkitt lymphoma/leukemia, multiple myeloma	*BCL7A*	Zani et al. (1996)
del(14)(q24q32)	Chronic lymphocytic leukemia, low-grade B-NHL	*ZFP36L1*	Pospisilova et al. (2007) and Nagel et al. (2009a)
t(14;15)(q32;q11–13)	Diffuse large B-cell lymphoma	*BCL8*	Dyomin et al. (1997)
t(14;16)(q32;q24)	B-ALL (L3), aggressive B-cell lymphoma, NOS	*CBFA2T3/ACSF3*	Salaverria et al. (2012)
t(14;16)(q32.33;q24.1)	Diffuse large B-cell lymphoma	*IRF8*	Bouamar et al. (2013) and Tinguely et al. (2014)
t(14;18)(q32;q21)*	Follicular lymphoma, diffuse large B-cell lymphoma	*BCL2*	Tsujimoto et al. (1985)
t(14;18)(q32;q21)	Marginal zone lymphoma	*MALT1*	Sanchez-Izquierdo et al. (2003) and Streubel et al. (2003)
t(14;19)(q32;q12)	Diffuse large B-cell lymphoma	*CCNE1*	Nagel et al. (2009b)
t(14;19)(q32;q13)	Diffuse large B-cell lymphoma	*SPIB*	Lenz et al.-2007
t(14;19)(q32;q13)*	B-cell chronic lymphocyticleukemia, other B-NHL	*BCL3*	Ohno et al. (1990)
t(14;22)(q32;q11)	Low-grade B-NHL	*IGL?*	Aamot et al. (2005)
t(X;14)(p11;q32)	MALT lymphoma	*GPR34*	Ansell et al. (2012)

Modified from Willis and Dyer (2000), Siebert et al. (2001), and Dyer (2013). Only those translocations are shown in which the partner genes have been identified by molecular cloning or equivalent technique(s). Several other IG translocations have been identified and in part FISH mapped, like t(14;19)(q32;p13) (Micci et al., 2007), but await unambiguous identification of the partners. *Variants with IG light-chain loci in 2p12 and 22q11 have been described.

The breakpoint on the derivative partner chromosome can be located 3′ or 5′ of the target oncogene because the transforming mechanism is deregulated expression through aberrant juxtaposition with the IG enhancer rather than creation of a gene fusion or promoter substitution. Enhancers can exert their activity over distances of several hundred kilobases. In BL, for example, the breakpoints affecting the *MYC* gene can be located up to almost 1 Mb centromeric of *MYC* in t(8;14) and telomeric of *MYC* in t(8;22) and t(2;8) (Joos et al., 1992a, 1992b; Einerson et al., 2006; Kroenlein et al., 2012). Remarkably, the breakpoints of the t(8;14) in 8q24 vary between endemic and sporadic BL with the former more frequently affecting the far 5′ (centromeric) part of the *MYC* locus (reviewed in Boxer and Dang, 2001; Küppers and Dalla-Favera, 2001). This variability of the breakpoints, which can also be observed in *MYC* translocations affecting non-IG loci, can pose considerable diagnostic problems if FISH is applied for their detection (Bertrand et al., 2007; May et al., 2010).

Gene deregulation may occasionally be a consequence of an insertion rather than a translocation. Thus, both *BCL2* and *CCND1* have been observed to be inserted into the *IGH* locus in cases of FL and MCL in rearrangements that functionally mimic the t(14;18) and t(11;14), respectively (Vaandrager et al., 2000; Fenton et al., 2004). Although the biological consequences of such insertions appear to be identical to those of regular translocations, their pathogenetic origins would appear to involve different DNA breaks.

Exceptions to the general rule that the recurrent translocations of mature lymphoid neoplasms rarely give rise to fusion genes occur predominantly in MALT lymphoma and T-cell lymphomas. In the former, the specific *t(11;18)(q21;q21)* leads to *API2–MALT1* fusion (Akagi et al., 1999; Dierlamm et al., 1999). In the latter, *t(2;5)(p23;q35)* as well as its rare variants lead to fusion of the anaplastic lymphoma kinase (*ALK*) gene in 2p23 with the nucleophosmin (*NPM*) gene or, in the case of variants, other partners (Morris et al., 1994). Finally, rare cases of peripheral T-cell lymphoma with an *ITK–SYK* fusion due to a *t(5;9)(q33;q22)* have been reported (Streubel et al., 2006b). Recent data from high-throughput sequencing studies suggest that a number of rare fusion genes remain to be discovered in lymphatic neoplasms.

The most common rearrangement of a non-IG locus in mature lymphoid neoplasms is the targeting of the *BCL6* gene in 3q27 that takes place in a variety of translocations with a multitude of chromosomal partners (Ueda et al., 2002a; Ohno, 2006) (Table 2.2). Common to all these translocations is that they lead to promoter substitution and, consequently, deregulation of the *BCL6* gene (Ohno,

2004, 2006; Jardin et al., 2007). Other oncogenes known to be targets of IG translocations are sometimes juxtaposed directly next to each other through translocations, such as *PAX5* and *MYC* through a t(8;9)(q24;p13) and *BCL6* and *MYC* through t(3;8)(q27;q24) in t(14;18)-positive FL (Bertrand et al., 2007; Sonoki et al., 2007; Johnson et al., 2009; Aukema et al., 2011). How the supposed *MYC* deregulation in these translocations occurs is so far unknown though an enhancer mechanism seems likely. There is no evidence for interposition of IG sequences like in t(8;14;18) (q24;q32;q21), a recurrent aberration in FL progression, in which both *MYC* and *BCL2* are deregulated from a common IG fragment between them (Dyer et al., 1996; Knezevich et al., 2005).

Table 2.2 | Chromosomal translocations affecting the *BCL6* locus in 3q27 in mature B-cell neoplasms

Translocation	Partner locus	*BCL6* partner gene	References
t(1;3)(q25;q27)	1q25	*GAS5*	Nakamura et al. (2008)
t(2;3)(p12;q27)	2p12	*IGK*	Bastard et al. (1992), Deweindt et al. (1993), and Akasaka et al. (2000a, 2000b)
t(3;3)(q25;q27)	3q25 3q26	*MBNL1* *SIATI*	Akasaka et al. (2003) Akasaka et al. (2003)
t(3;3)(q27;q27)	3q27	*ST6GAL1*	Akasaka et al. (2003)
t(3;3)(q27;q27)	3q27	*EIF4A2*	Yoshida et al. (1999) and Akasaka et al. (2003)
t(3;3)(q27;q29)	3q29	*TFRC*	Yoshida et al. (1999), Akasaka et al. (2000a, 2000b), and Chen et al. (2006)
t(3;4)(q27;p11–13)	4p11–13	*RhoH/TTF*	Dallery et al. (1995) and Akasaka et al (2000a, 2000b), (2003)
t(3;6)(q27;p22)	6p21–22	*HIST1H4I*	Akasaka et al. (1997), (2000a, 2000b),Kurata et al. (2002), and Schwindt et al. (2006)
t(3;6)(q27;p21)	6p21	*PIM1*	Yoshida et al. (1999), Akasaka et al.(2000a, 2000b), and Kaneita et al. (2001)
t(3;6)(q27;p21)	6p21	*SFRS3/SRP20*	Chen et al. (2001b) and Ohno (2006)
t(3;6)(q27;q15)	6q15	*U50HG/SNHG5*	Tanaka et al. (2000) and Akasaka et al. (2003)
t(3;7)(q27;p12)	7p12	*IKZF1*	Hosokawa et al. (2000) and Kaneita et al. (2001)
t(3;7)(q27;q32)	7q32	*MIR29/FRA7H*	Schneider et al. (2008)
t(3;8)(q27;q24.1)	8q24	*MYC*	Bertrand et al. (2007) and Sonoki et al. (2007)
t(3;9)(q27;p24)	9p24	*DMRT1*	Chen et al. (2006)
t(3;9)(q27;p11)	9p11	*GRHPR*	Akasaka et al. (2003)
t(3;11)(q27;q23)	11q23	*BOB1/OBF1/POU2AF1*	Galiègue-Zouitina et al. (1996) and Ohno (2006)
t(3;12)(q27;p13)	12p13	*GAPDH*	Montesinos-Rongen et al. (2003) and Chen et al. (2006)
t(3;12)(q27;q12)	12q12	*LRMP*	Akasaka et al. (2003)
t(3;12)(q27;q23–24)	12q23	*NACA*	Akasaka et al. (2000a, 2000b)
t(3;13)(q27;q14)	13q14	*LCP1*	Galiègue-Zouitina et al. (1999)
t(3;14)(q27;q32)	14q32	*IGH*	Bastard et al. (1992), Deweindt et al. (1993), Kerckaert et al. (1993), Ye et al. (1993b), and Akasaka et al. (2003)
t(3;14)(q27;q32)	14q32	*HSP89A*	Akasaka et al. (2000a, 2000b), Xu et al. (2000), Montesinos-Rongen et al. (2003), and Chen et al. (2006)
t(3;16)(q27;p13)	16p13	*CIITA*	Yoshida et al. (1999, Kaneita et al. (2001), and Akasaka et al. (2003)
t(3;16)(q27;p11)	16p11	*IL21R*	Ueda et al. (2002b)
t(3;19)(q27;q13)	19q13	*NAPA*	Akasaka et al. (2003)
t(3;22)(q27;q11)	22q11	*IGL*	Bastard et al. (1992), Deweindt et al. (1993), Miki et al. (1994b), and Schimanuki et al. (2013)

Data from http://atlasgeneticsoncology.org/Genes/BCL6ID20.html, Ueda et al. (2002a), and Ohno (2006). Chromosomal bands of *BCL6* partner genes and gene annotations may in individual cases be mapped to different chromosomal bands in various publications

Cytogenetic evolution in lymphoid neoplasms

Several cytogenetic and subsequent molecular genetic studies have led to the concept that the neoplastic process in many mature lymphoid malignancies follows a multistep model similar to that proposed for colorectal cancer and other malignancies. It is widely assumed that a primary genetic alteration of a tumor clone

initiates lymphomagenesis. Primary alterations are usually present in the stemline of a tumor. Chromosomal translocations, like several of the *IG* and *TCR* translocations, are most common as primary genetic alterations and can serve as valuable diagnostic markers. However, it should be noted that what in one disease setting may constitute a primary change in another may occur as a secondary abnormality.

As shown in mouse transgenic models, the primary genetic alteration is often not sufficient to drive lymphomagenesis (reviewed in Willis and Dyer, 2000). Moreover, by sensitive molecular techniques, several primary genetic alterations like t(14;18), t(11;14), or t(2;5) can also be detected in healthy individuals, sometimes at surprisingly high levels (Limpens et al., 1995; Maes et al., 2001; Bäsecke et al., 2002; Biagi and Seymour, 2002; Roulland et al., 2004, 2014). Although our understanding is limited as to what extent the cells carrying the translocations are susceptible to neoplastic transformation, it has been shown that the presence of t(14;18)-positive precursors is predictive for the later development of FL and the precursors can actually progress into FL (Roulland et al., 2014). These findings have contributed to the view that additional genetic changes are required for the full neoplastic phenotype of a mature lymphoid malignancy to emerge. The aberrations that bring about this phenotypic transformation are usually called secondary genetic changes. Consequently, the vast majority of lymphomas with a defined primary change, like t(14;18)- positive FL or t(11;14)-positive MCL, carry also secondary alterations (Johansson et al., 1995). The so-called tertiary genetic events may occur in some lymphomas and are associated with the transformation of an indolent malignancy to more aggressive forms. As will be described subsequently, secondary and tertiary chromosomal alterations in lymphoid malignancies predominantly lead to gain or loss of genetic material, whereas recurrent, balanced translocations—with the exception of translocations affecting the *MYC* locus in chromosome band 8q24—seem to be uncommon as secondary events. The number of secondary genetic aberrations, be they driver or passenger mutations, usually increases during disease progression (Knight et al., 2012; Beà et al., 2013; Landau et al., 2013; Bauer et al., 2014). As a rule of thumb, within a given lymphoma subtype, the prognosis is inversely related to the complexity of the karyotype or the extent of the secondary changes.

Secondary genetic aberrations may be present in only a subset of cells of a given tumor, and different secondary aberrations may be present in different subclones that may become the dominant clone during disease progression or at relapse (Knight et al., 2012; Landau et al., 2013; de Rossi et al., 2014). Tumors of the

same type (and harboring the same primary event) might thus show variation in terms of secondary aberrations. Nevertheless, the pattern of secondary changes in mature lymphoid neoplasms is not random but rather seems to depend on the nature of the primary event. Some primary genetic alterations like t(11;18)(q21;q21) are hardly ever associated with cytogenetically detectable secondary aberrations (Horsman et al., 1992; Ott et al., 1997; Barth et al., 2001). Other translocations such as t(1;14)(p22;q32) are associated with a highly conserved set of secondary events, including trisomy of chromosomes 3, 12, and 18. FL with t(14;18)(q32;q21) show different, distinctive patterns of secondary changes suggesting different pathways of germinal center B-cell transformation (Höglund et al., 2004). T-PLL is characterized by an extraordinary conservation of both primary and secondary genetic changes (reviewed by Dürig et al., 2007).

The mutational pattern in a given lymphoma might not only depend on the primary aberration but also on the mutational mechanisms active in this particular case (Alexandrov et al., 2013). Several mutational mechanisms have been shown to be operative in lymphomas contributing to the mutational landscape of the tumors. Indeed, the genome of a lymphatic neoplasm usually contains between 1000 and several thousand mutations (Puente et al., 2011; Richter et al., 2012; Alexandrov et al., 2013). Based on the mutational patterns detected, it has been shown for FL that disease progression can occur from the initial tumor or from a clonal progenitor not found at initial diagnosis (Okosun et al., 2014; Pasqualucci et al., 2014). Remarkably, at least in FL, chromosomal, molecular, and epigenetic changes seem to evolve, concordantly suggesting that a chromatin-acting factor like *CREBBP* or *MLL2* may be one of the regulators of clonal evolution (Loeffler et al., 2015). Tumor heterogeneity and its impact on progression and clinical outcome will become a major topic for future studies in lymphoma genetics (Knight et al., 2012; Schuh et al., 2012; Landau et al., 2013; Rossi et al, 2014; Suguro et al., 2014).

Chromosomal aberrations common to multiple subtypes of mature lymphoid neoplasms.

In the following sections, the most common cytogenetic changes in mature lymphoid neoplasms will be discussed in the context of the disease subtypes in which they are most prominent. It should nevertheless be emphasized that many aberrations are recurrent in several or even all kinds of mature lymphoid neoplasms. These might constitute primary aberrations in some of them but are more likely to be secondary or even tertiary aberrations in the majority. Probably, the best example of such a low-specific change is deletion of 6q.

Deletions of the long arm of chromosome 6 are frequent in all types of mature lymphoid neoplasms including HL. The incidence in different studies varies from roughly 5% in CLL to 30% in DLBCL up to even higher frequencies in T/NK-cell disorders. The deletions have mostly been interpreted as terminal. Band 6q21 seems to be the one most often affected. Offit et al. (1993) reviewed the chromosome 6 abnormalities in 459 consecutively ascertained karyotypically abnormal cases of NHL and suggested that three minimally common deleted regions could be discerned: a distal one encompassing 6q25–27, a second one involving the more proximal band 6q21, and the third one located between the two others involving band 6q23. Several loss of heterozygosity (LOH), molecular cytogenetic, and aCGH studies have meanwhile narrowed down critical regions in 6q to 6q21, 6q23.3, and 6q27. These studies have identified recurrent inactivation of the *PRDM1/BLIMP1* gene in 6q21 in activated B-cell-type (ABC-DLBCL) and T-cell lymphomas (Pasqualucci et al., 2006; Tam et al., 2006; Iqbal et al., 2009). Moreover, a minimally common deleted region in 6q23.3 containing the *TNFAIP3 (A20)* and *PERP* genes has been identified in FL and ocular adnexal marginal zone B-cell lymphoma (MZL), and mutations inactivating *TNFAIP3* have been detected in classical Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphomas (PMBCL) (Ross et al., 2007; Giefing et al., 2008; Honma et al., 2008; Schmitz et al., 2009).

The descriptions in this chapter will focus on chromosomal changes as they are detected by chromosome banding techniques. It needs to be stressed that the "real" frequencies of chromosomal aberrations may be underestimated if this approach is the only one taken, without help from molecular cytogenetic techniques like FISH and CGH, which can also be used to examine paraffin-embedded samples. Therefore, though the contribution of these techniques is not the prime concern of this book, data thus obtained will often be referred to as they have contributed mightily to the current picture of the cytogenetic changes of mature lymphoid neoplasms. For reviews focusing on the application of FISH and CGH in lymphoid neoplasms, the reader may be well advised to consult Martin-Subero et al. (2003a), Dewald et al. (2004), Kearney and Horsley (2005), Ventura et al. (2006), Wolff et al. (2007), and Kluin and Schuuring (2011). Finally, the exponentially fast-growing number of studies using aCGH and single-nucleotide polymorphism (SNP) chip-based technologies as well as next-generation sequencing will not be discussed in detail here. A review of the findings obtained by array-based technologies was published by Nieländer et al. (2007), and databasing of the findings has been initiated (http://www.progenetix. net/). For mutational patterns derived

from highthroughput sequencing, the reader is referred to constantly updated databases such as COSMIC http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/) and the reports from the ICGC project (http://www.icgc.org/).

Mature B-cell neoplasms

A comparative overview of the different subtypes of mature B-cell neoplasms recognized by the Kiel, REAL, and WHO classifications is provided in Table 2.3. The clinically most relevant chromosomal aberrations are summarized in Table 2.4.

FL (including pediatric FL and primary cutaneous follicle center lymphoma)

FL comprises 22% of all lymphomas worldwide but shows significant geographic variation. FL is rare in children, and the median age of incidence is 59 years. It is a neoplasm resembling follicle center B cells, that is, centrocytes and centroblasts. There is heterogeneity with regard to growth pattern (follicular, follicular and diffuse, and minimally follicular) and the proportion of centroblasts, the latter being reflected in three different grades (FL grades 1–3) with grade 1 showing the lowest numbers of centroblasts. Grade 3 shows the highest number of centroblasts and is subdivided into grade 3a in which centrocytes are present and grade 3b with solid sheets of centroblasts (Jaffe et al., 2001; Swerdlow et al., 2008). Variants include diffuse follicle center lymphoma and cutaneous follicle center lymphoma. Particularly, if considering the prominence of centroblasts in grade 3b and variants with diffuse growth patterns, it is not surprising that at this end of the morphologic spectrum, FL shows considerable overlap with DLBCL (Jaffe et al., 2001; Swerdlow et al., 2008). Moreover, there is a steady rate (3% per year) of transformation of FL mostly to DLBCL (Montoto et al., 2007; Montoto and Fitzgibbon, 2011). Finally, FL and DLBCL might coexist in a patient even in the same lymph node, rendering a clear distinction between the karyotypic features of the two diseases difficult. Approximately 80–90% of FL carry a *t(14;18) (q32;q21)* (Figure 2.2) or very seldom one of its variants, *t(2;18) (p12;q21)* or *t(18;22)(q21;q11)* (Johansson et al., 1995; Hillion et al., 1991; Bentley et al., 2005; Lin et al., 2008). It is noteworthy that the t(14;18) is extremely rare in FL patients below 18 years of age and virtually absent in children below the age of 14 years (Oschlies et al., 2010; Louissaint et al., 2012; Liu et al., 2013).

Table 2.3 | Comparison of the Kiel, REAL, and WHO classifications of B-cell malignancies*

Kiel classification	*REAL classification*	*WHO (2001)*	*WHO (2008)*
Peripheral B-cell neoplasms	Mature (peripheral) B cell neoplasms		
B-lymphocytic, B-CLL, B-PLL	B-CLL/B-PLL/small lymphocytic lymphoma	**B-CLL**/small lymphocytic lymphoma	**B-CLL**/small lymphocytic lymphoma
Lymphoplasmacytoid immunocytoma	Variant B-CLL: with plasmacytoid differentiation	Variant B-CLL: with monoclonal gammopathy/ plasmacytoid differentiation	Variant B-CLL: with monoclonal gammopathy/ plasmacytoid differentiation
		B-PLL	B-PLL
Lymphoplasmacytic immunocytoma	Lymphoplasmacytoid lymphoma	Lymphoplasmacytoid lymphoma	Lymphoplasmacytic lymphoma
Centrocytic	Mantle cell lymphoma	Mantle cell lymphoma	Mantle cell lymphoma
Centroblastic, centrocytoid subtype		Variant: blastoid	Morphologic variants: blastoid, pleomorphic, small cell, marginal zone-like
Centroblastic–centrocytic, follicular	Follicular center lymphoma, follicular grades I and II	**Follicular lymphoma, grades I and II**	**Follicular lymphoma, grades I and II**
Centroblastic–centrocytic, diffuse	Follicular center lymphoma, diffuse, small cell*		
Centroblastic, follicular	Follicular center lymphoma, follicular grade III	Follicular lymphoma, grade III	Follicular lymphoma, grade III
		Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma
	Extranodal marginal zone B-cell lymphoma (low-grade B-cell lymphoma or MALT)	**Extranodal marginal zone B-cell lymphoma of MALT type**	**Extranodal marginal zone B-cell lymphoma of MALT type**
Monocytoid lymphoma, including marginal zone lymphoma	Nodal marginal zone B-cell lymphoma*	Nodal marginal zone B-cell lymphoma*	Nodal marginal zone B-cell lymphoma*
	Splenic marginal zone B-cell lymphoma*	Splenic marginal zone B-cell lymphoma*	Splenic marginal zone B-cell lymphoma*
Hairy cell leukemia	Hairy cell leukemia	Hairy cell leukemia	Hairy cell leukemia
Plasmacytic	Plasmacytoma/myeloma	**Plasma cell myeloma/plasmacytoma**	**Plasma cell myeloma/plasmacytoma**
Centroblastic (monomorphic, polymorphic, and multilobated subtypes)	Diffuse large B-cell lymphoma	**Diffuse large B-cell lymphoma,** variants: centroblastic, immunoblastic, T cell/histiocyte rich, lymphomatoid granulomatosis type, anaplastic large B-cell, plasmablastic	**Diffuse large B-cell lymphoma, NOS**
			Morphologic variants: centroblastic, immunoblastic, anaplastic
			Subtypes: T cell/histiocyte rich
			Primary CNS
			Primary cutaneous, leg type
			EBV-positive DLBCL of the elderly
			Other: DLBCL associated with chronic inflammation
			Lymphomatoid granulomatosis type
			ALK+ DLBCL HHV8-
			Associated multicentric Castleman disease
B-immunoblastic			

Kiel classification	*REAL classification*	*WHO (2001)*	*WHO (2008)*
B-large cell anaplastic lymphoma			
	Primary mediastinal largeB-cell lymphoma	Subtypes: mediastinal (thymic) large B-cell, primary effusion lymphoma, intravascular large B-cell lymphoma	Primary mediastinal (thymic) large B-cell lymphoma
			Primary effusion lymphoma Intravascular large B-cell lymphoma
Burkitt lymphoma	Burkitt lymphoma	Burkitt lymphoma	Burkitt lymphoma
	High-grade B-cell lymphoma, Burkitt-like*	Burkitt cell leukemia	Burkitt cell leukemia/BALL L3
		Atypical Burkitt lymphoma	**B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL**

Data from Lennert et al. (1975), Harris et al. (1994), Jaffe et al. (2001), and Swerdlow et al. (2008).
Bold letters represent the most common subtypes.
*Provisional entity.

Pediatric-type FL is recognized as a distinct but provisional entity in the 2008 WHO classification (Harris et al., 2008; Swerdlow et al., 2008) and is characterized by the absence of *t(14;18)(q32;q21)* and *BCL6* rearrangements and an overall indolent clinical behavior (Oschlies et al., 2010; Louissaint et al., 2012; Attarbaschi et al, 2013; Martin-Guerrero et al., 2013). A subset of cases (mainly FL3 with or without DLBCL component) shows *IG–IRF4* translocations with frequent chromosomal imbalances (Salaverria et al., 2011, 2013). In FL lacking *IG–IRF4* translocations, two subgroups may be distinguished: one “genetically normal” group with no DLBCL component and no copy number abnormalities and a “genetically aberrant group” (often with a DLBCL component) with more frequent copy number abnormalities, LOH at 1p36, and recurrent *TNFRSF14* and *EZH2* mutations (Salaverria et al., 2011; Martin-Guerrero et al., 2013). Pediatric-type FL is also encountered in young adults; then too it is characterized by a high proliferation rate but indolent clinical behavior (Louissaint et al., 2012; Liu et al., 2013).

In primary cutaneous follicle center lymphoma, conflicting data on the frequency of t(14;18) have been published. Variations among studies may be related to differences among patient cohorts and technique used (PCR vs. FISH) to detect the translocation; however, if any real frequency differences exist at all, the translocation seems to be less common in cutaneous than in nodal FL (Mirza et al., 2002; Vergier et al., 2004; Kim et al., 2005; Streubel et al., 2006a; Belaud-Rotureau et al., 2008; Gulia et al., 2011; Abdul-Wahab et al., 2014).

In nodal FL, there is evidence that the t(14;18) is more frequent in FL grades 1 and 2 (88% according to Katzenberger et al., 2004) than in FL 3, particularly FL 3b. Horn et al. (2011) identified using FISH *BCL2* breaks in 22/25 (88%), 7/12 (58%), and 2/23 (9%) of FL1/2, FL3A, and FL3B, respectively. Ott et al. (2002) found t(14;18) in 8 of 11 (73%) FL3a but only in 2 of 16 (13%) FL3b with or without a DLBCL component. Similarly, Katzenberger et al. (2004) found t(14;18) in only 1 of 27 FL3b (4%). Bosga-Bouwer et al. (2003) claimed the existence of three distinctive subgroups of FL3b based on the presence of breakpoints in 3q27, a translocation t(14;18), or the absence of both. None of their FL grade 3B cases harbored both a t(14;18) and a 3q27 aberration. Indeed, *trisomy 3* and *breakpoints in 3q27* affecting the *BCL6* locus are the most prominent findings in t(14;18)-negative FL. As there is convincing evidence for a biological difference between t(14;18)-positive and t(14;18)- negative FL, these two groups will in the following be treated separately (Leich et al., 2009).

The nonrandom occurrence of *t(14;18)(q32;q21)* in NHL was first pointed out by Fukuhara et al. (1979). Yunis et al. (1984) mapped the breakpoints to subbands 14q32.3 and 18q21.1. The t(14;18) has since turned out to be the most common translocation in NHL (15% of the total) but with considerable geographic differences (Biagi and Seymour, 2002). When tested for molecularly, the translocation can also be detected in tissues from healthy donors to some extent depending on their age and external factors such as smoking habits and exposure to pesticides (Limpens et al., 1995; Biagi and Seymour, 2002; Roulland et al., 2004; Agopian et al., 2009; Tellier et al., 2014). t(14;18) is not restricted to FL but may also be detected in 30% of DLBCL. In that lymphoma, the translocation seems to be largely restricted to the germinal center B-cell-like type (GCB) as defined by gene expression profiling (Rosenwald et al., 2002; Visco et al., 2013). The frequent

Table 2.4 | Overview of frequent and diagnostically relevant chromosomal aberrations in the most common mature B-lymphoid neoplasms

Neoplasm	*Cytogenetic aberration*	*Frequency (%)*
B-cell chronic lymphocytic leukemia/small lymphocytic	del(13q)	~50
	+12	~15
lymphoma	del(11q)	15–20
	del(6q), del(17p)	~5
	t/der(14)(q32)	4–20
Mantle cell lymphoma	t(11;14)(q13;q32)	>95
	del(11q), del(13q), der(3q)	10–50
	+12, del(1p), del(6q), del(9p), del(17p)	5–15
Extranodal marginal zone B-cell lymphoma of MALT type	t(14;18)(q32;q21) involving MALT1	11
	t(3;14)(p14;q32)	<10
	t(1;14)(p22;q32)	<2
	+3/3q, +18/18q	30
Follicular lymphoma	t(14;18)(q32;q21) and variants involving BCL2	80–90
	t(3q27)	<10 (FL1/2)–55 (FL3b)
	+X, +7, +12/12q, +18/18q, +der(18)	
	t(14;18), del(6q), del(10q), del(17p), dup(1q), der(1p	>10
Diffuse large B-cell lymphoma	t(3q27)	20–40
	t(14;18)(q32;q21)	20–30 (GCB)
	t(8;14)(q24;32)/t(8q24)	5–15 (GCB > ABC)
	+3/3q, +18/18q, +19q, del(6q), del(9p)	10–40 (ABC)
	+1q, +2p13–16, +7, +11q, +12/12q	10–40 (GCB)
	+9/9p23–24, +2p13–16	50–90 (PMBCL)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL	t(8q24)/MYC	
	t(14;18)/IGH–BCL2	
	t(3q27)/BCL6	
Burkitt lymphoma	t(8;14)(q24;q32) and variants	100
	dup(1q)	~30–50
	+7, +12	~10–30
Plasma cell myeloma/ plasmacytoma	t(4;14)(p16;q32), t(11;14)(q13;q32), t(14;16)(q32;q23)	~20
	t(6;14)(p25;q32), t(8;14)(q24;q32)	5
	Other t(14q32)	
	Total t(14q32)	~40–60
	−13, del(13q)	15–50
	dup(1q), del(6q), del(11q)	5–20

transformation of FL to DLBCL has led to the suggestion that perhaps those diffuse lymphomas that carry a t(14;18) are the ones that have evolved from follicular NHL (Kneba et al., 1991).

The t(14;18)(q32;q21) in FL juxtaposes the *BCL2* oncogene next to the *IGH* locus (Tsujimoto et al., 1984). In molecular terms, the translocation is therefore different from the cytogenetically identical aberration involving *MALT1* in MALT lymphomas. In FL, the 18q21 breaks in 60–70% of the cases cluster within a 2.8 kb major breakpoint region (MBR) located in an untranslated part of the third and last (3′) exon of *BCL2*; most of these breaks occur within much smaller subregions of the MBR (reviewed by Willis and Dyer, 2000; van Dongen et al., 2003). Some 10% of the breakpoints are found in the more distal minor cluster region (MCR). Variant breakpoints have also been described, including 3′ *BCL2* (12%)

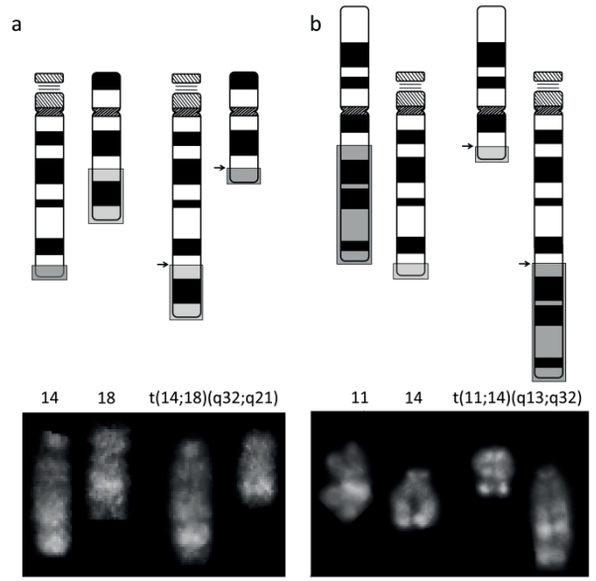

Figure 2.2 | Translocations t(14;18)(q32;q21) and t(11;14) (q13;q32). Fluorescence R-banding. (A) Ideogram and partial karyotype with t(14;18)(q32;q21) involving *IGH* and *BCL2*. (B) Ideogram and partial karyotype with t(11;14)(q13;q32) involving *IGH* and *CCND1*.

and 5′ MCR (6%) (Buchonnet et al., 2000, 2002). The breakpoints in the *IGH* locus fall within the region containing the *J*-segments. Indeed, the translocation is supposed to originate from a failed *VDJ* rearrangement, which in turn argues that this lymphoma derives from a precursor cell in the bone marrow rather than from a germinalcenter cell. Remarkably, the t(14;18)-positive clone seems to be characterized by considerable plasticity allowing the tumor cells to become microvascular endothelial cells (Streubel et al., 2004). The *BCL2* gene deregulated by the translocation encodes an inhibitor of apoptosis (for reviews, see Thomadaki and Scorilas, 2006; Zinkel et al., 2006; Letai, 2008). A subset of t(14;18)-positive lymphomas do not express intact BCL2 due to somatic mutations of the gene (Schraders et al., 2005; Johnson et al., 2009; Adam et al., 2013). Vice versa, BCL2 expression is not restricted to tumor cells of FL but can be observed in a wide range of B-cell lymphoid neoplasms including CLL and DLBCL.

Less common variants of t(14;18) are the *t(2;18) (p12;q21)* and *t(18;22)(q21;q11)* that juxtapose the *BCL2* gene next to the *IGK* and *IGL* loci, respectively (Lin et al., 2008). The breakpoints in these variants are located in the 5′ end of the *BCL2* locus and not in the 3′ end that typically is involved in t(14;18) (Adachi et al., 1990; Hillion et al., 1991). Like t(14;18), both these translocations also occasionally occur in CLL, mostly secondarily to trisomy 12 (Leroux et al., 1991; Bentley et al., 2005). Indeed, they might even be more common in that disease (Adachi et al, 1990; Lin et al., 2008). Due to their rarity, it is not yet proven whether FL with these variants show the same clinical course as do t(14;18)-positive FL.

Only in 10% of t(14;18)-positive cases is this the sole cytogenetic change (Johansson et al., 1995). Recurrent secondary alterations seen in 10% or more are + X, +1q21–44, +7, +12q, +18q, del(1)(p36), del(6q), del(10)(q22–24), and the development of polyploidy. The most frequent secondary event arising after the t(14;18) seems to be the duplication of the der(18)t(14;18) (Johansson et al., 1995; Horsman et al., 2001; Höglund et al., 2004; Aamot et al., 2007). The secondary chromosomal changes in t(14;18)-positive FL arise nonrandomly and in an apparently distinct temporal order. Four possible cytogenetic pathways have been shown to characterize the early stages of clonal evolution, which converge on a common route during later stages. Based on these pathways, FL with t(14;18) may be classified into cytogenetic subgroups defined by the presence or absence of 6q−, +7, or + der(18)t(14;18). These subgroups do not seem to be associated with distinctive prognostic features, however (Höglund et al., 2004).

The most prominent changes in t(14;18)-negative FL are numerical and structural *changes of chromosome 3*. Horsman et al. (2003) showed the average number of chromosomal aberrations to be similar in t(14;18)-positive and t(14;18)-negative FL, namely, 7.9 and 8.2, respectively. *t(14q32)* other than t(14;18) is present in 28% of t(14;18)-negative FL. *Rearrangements of 1p36* are significantly less frequent than in t(14;18)-positive FL (8% versus 18%), whereas *trisomy 3* is significantly more frequent (17% vs. 2%). Trisomy 3 may be part of a distinct cytogenetic pattern in t(14;18)-negative FL, which also includes *trisomy 18*. As described earlier, trisomies for chromosomes 3 and 18 are quite common in marginal zone lymphomas, and it must be questioned whether some of the +3 and +18 single- or double-positive lymphomas are not indeed marginal zone lymphomas with a follicular growth pattern rather than true FL.

In line with the higher frequency of FL grade 3 in t(14;18)-negative FL, several studies have documented *t(3q27)* to be highly recurrent in this disease. Horsman et al. (2003) found that *t(3;14) (q27;q32)* was significantly more frequent in lymphomas without than with t(14;18). The overall frequency of t(3q27) has been reported to be below 10% in t(14;18)-positive FL and FL of grades 1 and 2 but to reach 55% in FL3b with a DLBCL (Horsman et al., 2003; Katzenberger et al., 2004; Horn et al., 2011). In contrast to t(14;18)-positive FL, t(3q27)-positive FL less frequently express CD10 and BCL2 (Jardin et al., 2002).

The target of t(3q27) is *BCL6*, which encodes a transcriptional regulator involved in germinal center formation (Jardin et al., 2007). The *BCL6* (formerly also called *BCL5* or *LAZ3*) gene was identified through cloning of the recurrent t(3;14) (q27;q32) involving *IGH* and was shown to be involved also in its light-chain variants *t(2;3) (p12;q27)* and *t(3;22)(q27;q11)* (Kerckaert et al., 1993; Ye et al., 1993a, 1993b; Miki et al., 1994a, 1994b). A steadily growing number of other t(3q27) translocations and intrachromosomal changes in chromosome 3 are also being cytogenetically identified and molecularly characterized, all of which juxtapose *BCL6* next to various partners (Table 2.2); for referencing and steady updates, the reader is referred to http://atlasgeneticson cology.org/Genes/BCL6ID20.html. Indeed, *BCL6* seems to be one of the most promiscuous loci in B-cell lymphomas, and translocations affecting 3q27 are highly recurrent in various subtypes of Bcell disorders including particularly DLBCL or nodular lymphocyte predominance HL (discussed subsequently). The common theme of all these translocations is that the *BCL6* promoter is substituted by the promoter of the partner that interrupts its negative autoregulation, a similar effect to that re-

ported for somatic *BCL6* mutations (Chen et al., 1998; Pasqualucci et al., 2003). Despite this supposed common mechanism of action, considerable molecular heterogeneity of the breakpoints has been observed. First, an MBR in the 5′ region of the gene is distinguished from the alternative breakpoint region (ABR) that is located more than 200 kb telomeric (Butler et al., 2002). With regard to the latter, it has not yet been ruled out that also other genes or regulatory elements than *BCL6* may be involved. Remarkably, *BCL6* breakpoints in t(14;18)- negative FL seem to predominantly affect the ABR, whereas those in DLBCL mostly affect the MBR (Bosga-Bouwer et al., 2005; Gu et al, 2009). Though the vast majority of t(3;14)(q27;q32) affects the constant regions of the *IGH* locus, switch gamma translocations seem to be more prominent in FL (70%), whereas switch μ translocations are more frequent in DLBCL (89%) (Ruminy et al., 2006).

A distinctive subtype of t(14;18)-negative FL is characterized by a predominantly diffuse growth pattern and deletions in 1p36 (Katzenberger et al., 2008, 2009).

Clinical correlations and disease progression in FL

The early steps of clonal evolution and disease progression during lymphomagenesis have to be distinguished from the secondary changes that take place when already manifest FL transform to either higher-grade FL or high-grade NHL (e.g., DLBCL or DLBCL–BL intermediate). Several features are notable regarding the initial steps of FL lymphomagenesis:

1. The t(14;18)(q32;q21) can, in up to two-thirds of healthy individuals, be detected in nonmalignant B cells in the peripheral blood. Multiple clones may be present and can persist and expand over time (Limpens et al., 1995; Roulland et al., 2006a, 2014). The t(14;18) can also be found in reactive lymphoid tissue of healthy individuals (Limpens et al., 1991). At present, these cells may best be described as “follicular lymphoma-like cells” (FLLCs) (Roulland et al., 2006b).

2. The t(14;18)-positive FLLCs (and possibly also follicular lymphoma *in situ* (FLIS) cells; see following text) probably are able to reenter the germinal center and undergo additional rounds of somatic hypermutation there, after which they may circulate between the germinal center and bone marrow (Roulland et al., 2006b; Kluin, 2013). The recently identified t(14;18)-positive germinal center B cells represent an important missing link between the FLLCs and FLIS (see following text) (Kluin, 2014; Tellier et al., 2014).

3. So-called FLIS has been observed in lymph nodes from healthy individuals (Cong et al., 2002). These FLIS show strong BCL2 expression but preservation of the nodal architecture. During the progression from FLIS to manifest FL, an increase in (epi)genomic complexity has been observed (Mamessier et al., 2014; Schmidt et al., 2014).

A model of nonpediatric FL has emerged, suggesting at least two cytogenetic pathways during the progression of manifest lymphomas:

FL grades 1 and 2 with t(14;18) can progress to FL3a when secondary changes occur or transform to secondary DLBCL through the acquisition of tertiary aberrations of, for example, 17p (*TP53*), 9p21 (*CDKN2A*), or 8q24 (*MYC*) (Christie et al., 2008). Transformation is mostly associated with an unfavorable prognosis (Johnson et al., 2008).

FL, mostly of grade 3b and lacking t(14;18) but frequently showing t(3q27), can also progress to DLBCL through pathways similar to those of the first group (Bosga-Bouwer et al., 2005, 2006). As for the (cytogenetic) pattern of clonal evolution, two main pathways can be distinguished: One includes linear clonal evolution in which the relapse arises from the previous FL clone (with the acquisition of additional genetic aberrations). The other involves divergent clonal evolution where the relapse originates from an FL precursor common to the tumor present at relapse and the preceding FL (Höglund et al., 2004; Berglund et al., 2007; Johnson et al, 2008; Green et al., 2013; Okosun et al., 2014; Pasqualucci et al., 2014; Loeffler et al., 2015). In addition to t(14;18), mutations of *CREBBP* and *MLL2* seem to be early events in FL lymphomagenesis.

A variety of cytogenetic and molecular cytogenetic studies have correlated chromosomal changes in FL with outcome. Tilly et al. (1994) showed that structural alterations of 1p21–22, 6q23–26, 4q, and 17p were significantly associated with reduced 5- year survival in FL. In t(14;18)-positive FL, del(1) (p36), del(6q), del(10)(q22–24), +7, the total number of abnormalities, the number of markers and additions, and the presence of polyploidy have been correlated with morphologic progression. In t(14;18)-positive FL, Höglund et al. (2004) reported +X, 1p−, +1q, +12, 17p−, and 17q− to be correlated with an unfavorable outcome in univariate analysis and +12 and del(17p) also correlated with poor survival in a multivariate analysis that included clinical risk factors. In male patients, gain of the X chromosome (as assessed by karyotyping and/or array CGH) correlated

with poor outcome (Johnson et al., 2008; Eide et al., 2010; Bouska et al., 2014). A cCGH study identified loss of 6q25–27 as being associated with unfavorable prognosis (Viardot et al., 2002), and recent aCGH-based reanalyses confirmed these findings and also suggested that deletions of 9p21 and gain of 11q are unfavorable prognostic markers (Schwaenen et al., 2009). In addition, high-resolution analysis has identified common sites of copy number-neutral LOH including 1p36 (with concomitant somatic mutations in *TNFRSF14*), 6p, 12q, and 16p (Cheung et al., 2010a, 2010b, 2012). *TNFRSF14* and *TP53* mutations have been associated with a worse prognosis (O'Shea et al., 2008; Cheung et al., 2010b). Gain/amplification of 2p15–16.1 (including the *REL* oncogene) may play a role in the transformation of FL to DLBCL (Kwiecinska et al., 2014). Several recent whole-genome and whole-exome sequencing studies have indicated an important role for chromatin modifiers, including *MLL2, CREBBP*, and *EZH2*, as driver and accelerator mutations in FL transformation (Green et al., 2013; Okosun et al., 2014; Pasqualucci et al., 2014). tDLBCL are more related to GCB-DLBCL than to ABC-DLBCL (Kwiecinska et al., 2014; Pasqualucci et al., 2014). All these studies should be regarded with some caution, however, since they were all retrospective and heterogeneous with regard to both treatment and t(14;18) positivity. Studies of large series of randomized FL patients in prospective trials are still lacking as are studies taking into account the gene expression risk profiles characteristic of this disease (Dave et al., 2004).

Diffuse large B-cell lymphoma (DLBCL)

DLBCL are a morphologically, biologically, and clinically heterogeneous group that constitutes 30–40% of all B-cell lymphomas. Based on the site of involvement, some entities such as primary DLBCL of the CNS and leg-type primary cutaneous DLBCL are distinguished from systemic DLBCL (Jaffe et al., 2001; Swerdlow et al., 2008). Hardly any chromosomal data exist on these site-specific diseases, but interphase cytogenetic studies have indicated a similar spectrum of changes to that of systemic DLBCL (Hallermann et al., 2004a, 2004b).

Some quantitative differences may nevertheless exist, as more than 30% of leg-type DLBCL have been shown by FISH to have t(8;14)(q24;q32) or variants and also in the plasmablastic and immunoblastic variant was t(8q24) often seen by interphase cytogenetics (Hallermann et al., 2004a; Kanungo et al., 2006; Belaud-Rotureau et al., 2008; Aukema et al., 2014; Siebert et al., unpublished results). In addition, deletions of 6p21 involving the MHC region are reported in over 50% of lymphomas of immune-privileged sites (primary CNS and testicular

lymphomas) and are more common compared to nodal DLBCL (Riemersma et al., 2000; Booman et al., 2006, 2008; Schwindt et al., 2009). In primary lymphoma of the bone, gains of 1q and amplification of 2p16.1, both associated with a germinal center-like genetic profile, have been identified (Heyning et al., 2010).

Another subtype, ALK-positive DLBCL, in which the tumor cells show a typical immunoblastic morphology with expression of VS38 and IgA, was recognized based on the expression of anaplastic lymphoma kinase. These lymphomas are cytogenetically characterized by a simple or complex t(2;17)(p23;q23) involving the clathrin (*CLTC*) gene in 17q23 and the *ALK* gene in 2p23 (Chikatsu et al., 2003; Gascoyne et al., 2003; Gesk et al., 2005). They typically lack *MYC* rearrangements but instead show *MYC* gain and amplification (Valera et al., 2013).
Cytogenetic data on T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), an additional morphologic subtype of DLBCL, are scarce. CGH analysis of 17 THRLBCL showed genomic imbalances in all cases. The most common imbalances were gain of Xq, 4q13–28, Xp11–21, and 18q21 and loss of 17p (Franke et al., 2002).

The nodal and extranodal types of DLBCL mostly show centroblastic or immunoblastic morphology (Jaffe et al., 2001). These common DLBCL must be distinguished from primary mediastinal (thymic) large B-cell lymphoma (PMBCL) (Jaffe et al., 2001). Gene expression studies have shown the latter to be associated with a distinct expression signature related to that of cHL (Rosenwald et al., 2003; Savage et al., 2003). Various expression subgroups of DLBCL were also identified by these studies. Clinically, most relevant were two subgroups of DLBCL identified by gene expression profiling named according to the COO signature, that is, ABC-DLBCL associated with an unfavorable and GCB-DLBCL associated with a more favorable outcome (Alizadeh et al., 2000; Rosenwald et al., 2002; Gutierrez-García et al., 2011).

No chromosomal aberration is completely specific for DLBCL, but many of the generally lymphoma-associated rearrangements are prominent also in this disease subtype. t(3q27), involving the *BCL6* locus and various partners in a manner similar to that in FL, is seen in 20–40% of DLBCL (Table 2.2). Iqbal et al. (2007) detected *BCL6* translocations at the MBR by FISH in 25 (19%) of 133 DLBCL cases, with a higher frequency in PMBCL (33%) and ABC-DLBCL (24%) than in GCB-DLBCL (10%).

Translocations of 14q32 involving the *IGH* locus can be detected in up to half of all DLBCL (Lenz et al., 2007; Bouamar et al., 2013). Approximately 20–30% of

DLBCL show a t(14;18)(q32;q21) (Rosenwald et al., 2002; Hummel et al., 2006; Barrans et al., 2010; Visco et al., 2013). These cases are predominantly centroblastic and belong almost exclusively to the GCB-DLBCL subtype (Schlegelberger et al., 1999; Rosenwald et al., 2002; Iqbal et al., 2004; Visco et al., 2013). A t(8;14) (q24;q32) or variant t(8q24) can be detected in around 10% of DLBCL, some of which, especially (pediatric) cases with an *IG–MYC* translocation and lacking *BCL2* and *BCL6* rearrangements, might represent true BL based on their gene expression profile (Dave et al., 2006; Hummel et al., 2006; Klapper et al., 2008a; Aukema et al., 2014). In others, these translocations are supposed to be secondary changes mostly associated with a very aggressive clinical behavior and in part related to transformation into lymphomas intermediate between DLBCL and BL (see following text). In addition to t(3;14)(q27;q32) and the light-chain variants t(2;3)(p12;q27) and t(3;22)(q27;q11) involving *BCL6* and the *MYC*-targeting translocations more typical of BL, a steadily increasing number of other t(14q32) with various partners also exist (Lenz et al., 2007; Bouamar et al., 2013), particularly in the ABC-DLBCL tumor subset (Lenz et al., 2007).

Frequently recurring numerical chromosome aberrations in DLBCL include gains of chromosomes X, 3, 7, 12, and 18 and losses of the Y chromosome and chromosomes 6, 13, 15, and 17. Based on cytogenetic data, commonly gained chromosomal regions are 1q23–31, 3q21–22, 6p, 7p, 7q31–32, 8q22–24, 11q12–13, 12q14–24, and 18q11–21 in centroblastic lymphomas and 1q21– 25, 3p24–21, 6p21, 7p12–21, 18q, and 22q12-qter in immunoblastic lymphomas. Commonly deleted chromosomal regions are 1p35-pter, 2p23-pter, 6q21–22, 6q25-qter, 8p12-pter, 9p21-pter, 11q23- qter, 12p12–13, and 17p12–13 in centroblastic lymphomas and 1p35–36, 2q22–24, 4q32-qter, 6q21–25, 7q33, 8q21, 9p24, 9q21–32, 11q21-qter, 14q23-qter, 16p13, and 18q21-qter in immunoblastic lymphomas. These imbalances mostly occur as part of complex karyotypes with many unbalanced translocations. Losses of the whole chromosome 10, deletions in 8q and 14q, as well as structural abnormalities of 4q have been reported to be significantly more frequent in immunoblastic than in centroblastic lymphomas (Johansson et al., 1995; Schlegelberger et al., 1999).

CGH studies suggest that the main effect of the vast majority of cytogenetic changes in DLBCL is to create a set of common imbalances that may, at least in part, form the basis for the subgroups of DLBCL defined by gene expression. ABC-DLBCL frequently show trisomy 3, gains of 3q (including *BCL6*), 18q21–22 (including *MALT1* and mostly *BCL2*), and 19q13 (including *SPIB*), but losses of

9p21 (including *CDKN2A*) and 6q21–22. GCBDLBCL show frequent gains of 1q, 2p13–16 (including *REL/BCL11A*), chromosome 7, 11q, and 12q12, whereas PMBCL show gains of 9p21-pter (including *JAK2/PDL2*) and 2p14–16 (including *REL/BCL11A*) (Bea et al., 2005; Tagawa et al., 2005; Kimm et al., 2007; Wessendorf et al., 2007; Lenz et al., 2008; Green et al., 2014). It should be stressed that complete or partial trisomy 9 with a minimal region of gain in 9p23–24 seems to be specific for PMBCL (Bentz et al., 2001). In general, specific chromosomal alterations might be associated with significant changes in gene expression signatures that reflect various aspects of lymphoma cell biology as well as the host response to the lymphoma (Bea et al., 2005).

Next-generation sequencing analyses have revealed a large number of potentially targetable, recurrently mutated genes including *MLL2, TP53, TNFRSF14, CARD11, GNA13, CD79B, EZH2, MYD88,* and *CREBPP* (Ngo et al., 2011; Pasqualucci et al., 2011a, 2011b; Lohr et al., 2012; Morin et al., 2013; Zhang et al., 2013; Bohers et al., 2014; Vaqué et al., 2014). Some of these are associated with one of the COO types, for example, *EZH2* (15–30%) and *GNA13* (15–30%) mutations in GCB-DLBCL and *MYD88* (20–35%) and *CD79B* (15–20%) mutations in ABC-DLBCL (Morin et al., 2011; Ngo et al., 2011; Pasqualucci et al., 2011a; Zhang et al., 2013; Bohers et al., 2014).

Clinical correlations in DLBCL

All clinical correlations in DLBCL have to be treated with extreme caution since the data derive from before the introduction of anti-CD20 antibody therapy (Rituxan). Moreover, established clinical risk factors including International Prognostic Index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993), subtyping by gene expression profiling, and evaluation in the context of other chromosomal aberrations were mostly not taken into account. The data on the prognostic importance of t(14;18) (Barrans et al., 2003; Akyurek et al., 2012; Visco et al., 2013; Bellas et al., 2014) and t(3q27) (Akasaka et al., 2000b; Barrans et al., 2002; Ueda et al., 2002a; Niitsu et al., 2007; Shustik et al., 2010; Akyurek et al., 2012; Akay et al., 2014) are conflicting; at present, no convincing evidence exists that one or the other is reliably linked to prognosis. Like in many other lymphomas, there is good evidence that del(17p) and del(9)(p21) in DLBCL are associated with progression and unfavorable prognosis (Tagawa et al., 2005). In centroblastic DLBCL, deletions and duplications of 1q have been reported to be adverse risk factors independent of IPI, whereas trisomy 5 and changes of 15q seem to be independent indicators of a reduced risk. In immunoblastic lym-

phomas, changes of 7q and 8q had a stronger impact on survival than did the IPI (Schlegelberger et al., 1999). Gains of *MAPKAPK3* located at 3p21.31 and loss of 9p21.3 (*CDKN2A/B*) have been associated with chemoresistance in DLBCL patients treated with immunochemotherapy (Kreisel et al., 2011). Interestingly, another study using array CGH found that clonal heterogeneity and 9p21.3 loss were associated with poor prognosis (Suguro et al., 2014). In addition to genomic imbalances, also aberrant DNA methylation has been shown to have prognostic impact with heavily methylated DLBCL cases showing a worse clinical outcome (Chambwe et al., 2014).

Recent advances in gene expression profiling and assessment of cytogenetic imbalance patterns offer new ways to classify lymphomas into prognostically meaningful subgroups based on their COO (Masque-Soler et al., 2013). Gains of 3p11– 12 provide prognostic information independently of the gene expression data (Bea et al., 2005). It is not likely, however, that this way of subgrouping patients exhausts the possibilities for clinically meaningful classification. DLBCL can show considerable molecular genetic heterogeneity, including aberrant somatic hypermutation of *IGH, BCL6, MYC,* and other genes (Pasqualucci et al., 2001). This and frequent uniparental disomy and epigenetic changes are biological parameters also likely to influence outcome. The adverse prognostic impact of *MYC* (in combination with additional *BCL2* and/or *BCL6*) rearrangements in DLBCL has been demonstrated in multiple FISH studies (Klapper et al., 2008b; Savage et al., 2009; Barrans et al., 2010; Aukema et al., 2014; Tzankov et al., 2014). It is therefore advisable to screen all DLBCL in routine diagnostic situations for *MYC* and related breakpoints with both break-apart and dualcolor dual fusion probes, in addition to performing chromosome banding analysis with karyotyping (Klapper et al., 2008b; Savage et al, 2009; Barrans et al., 2010; May et al., 2010; Kluin and Schuuring, 2011; Aukema et al., 2011, 2014; Tzankov et al., 2014). In the near future, these molecular cytogenetic analyses will likely be combined with targeted panel sequencing for diagnostic and prognostic relevant genes and COO classification using dedicated gene expression profiling.

Other large B-cell lymphomas

Other very rare entities of large B-cell lymphoma include intravascular large B-cell lymphoma (ILBL) and primary effusion lymphoma (PEL) (Jaffe et al., 2001; Swerdlow et al., 2008). In the former disease, hardly any cytogenetic studies have been reported though the presence of t(11;14)(q13;q32), t(14;18) (q32;q21), and *BCL6* rearrangements has been described in single cases (Vieites et al.,

2005; Rashid et al., 2006; Cui et al., 2014). A recent review by Mandal et al. (2007) suggested that structural aberrations of chromosomes 1, 6, and 10 and, less frequently, chromosomes 4, 5, and 8 might be nonrandom changes with a recurrent site of deletion in 6q21–24. PEL is universally associated with human herpes virus 8 (HHV-8)/Kaposi sarcoma herpesvirus (KSHV) infection. Also, EBV is found in most cases. Cytogenetic analyses mostly show a complex karyotype with structural rearrangements frequently involved in lymphomas in general but without subgroup-specific abnormalities (Boulanger et al., 2001). Trisomy 7, trisomy 12, and aberrations proximally in the long arm of chromosome 1 seem to be recurrent (Wilson et al., 2002). A CGH study identified recurrent gains of the X chromosome and 12q (Mullaney et al., 2000). In another array CGH study, copy number abnormalities involving, among others, 1q, 7q, 8q, 14q32, and chromosome 12 were identified with *SELPLG/ CORO1C* at 12q24.1 showing amplification/lowlevel gain in 23% of the cases (Luan et al., 2010).

The majority of PEL occur in the setting of HIV infection, which is associated with an increased risk of lymphoma. AIDS-related lymphomas include systemic lymphomas, mostly DLBCL and BL, primary central nervous system lymphomas (PCNSL), PEL, and plasmablastic lymphoma of the oral cavity (Jaffe et al., 2001; Swerdlow et al., 2008). AIDS-related and other lymphomas in immunodeficient patients show a spectrum of chromosomal aberrations similar to that of their counterparts in immunocompetent patients (Vaghefi et al., 2006). Activation of *MYC* and inactivation of *TP53* in conjunction with EBV and other viral infections seem to play a major pathogenetic role (Carbone, 2003). In line with these molecular changes, there seems to be a trend toward more complex karyotypes and a higher frequency of t(8;14)(q24;q32) and the variant translocations t(2;8) and t(8;22). In lymphomatoid granulomatosis, which is also an Epstein–Barr virus (EBV)-driven lymphoproliferative disorder for which immunodeficient patients carry an increased risk, no cytogenetic aberrations have yet been identified in line with the oligo- or polyclonal origin documented particularly in low-grade cases (Jaffe et al., 2001; Swerdlow et al., 2008).

Burkitt lymphoma (BL)

BL is a highly aggressive disease often presenting at extranodal sites or as an acute leukemia. It is the most common B-cell lymphoma in the pediatric age group but is also observed in the adult population (Boerma et al., 2004; Leoncini et al., 2008). Endemic and sporadic BL are recognized as variants manifesting differences in clinical presentation and biology. Immunodeficiency-associated BL is seen primarily in association with HIV infection.

The cytogenetic hallmark of BL is the t(8;14) (q24;q32) and its variants, t(2;8) (p12;q24) and t(8;22)(q24;q11). These translocations are present both in the endemic, African tumor type and in the sporadic BL occurring in Europe, America, and Japan, both in EBV-infected patients and in EBVnegative BL. The t(8;14) is present in 75–85% of all BL (Johansson et al., 1995). In 15–25%, one of the variant translocations is found with the t(8;22) occurring twice as frequently as t(2;8) (Figure 2.3).

BL was the first lymphoid neoplasm in which the underlying chromosomal rearrangement was characterized. The first cytogenetic study of BL was reported in 1963 by Jacobs and coworkers. After the introduction of banding techniques, Manolov and Manolova (1972) described an additional band at the end of 14q in five of six fresh BL and in seven of nine cell lines from such tumors. The nature of the BL-specific abnormality was clarified by Zech et al. (1976), who established that the 14q+ arose through the translocation t(8;14)(q24;q32). Based on a high-resolution study, Manolova et al. (1979) reported that the translocation was reciprocal. Further scrutiny of prophase–prometaphase cells from the BL-derived cell line Daudi allowed Zhang et al. (1982) to map the translocation breakpoints to subbands 8q24.13 and 14q32.33. Berger et al. (1979) described the first variant translocation, t(8;22)(q24;q11), and Miyoshi et al. (1979) and van den Berghe et al. (1979) simultaneously reported the second variant, t(2;8)(p12;q24).

The molecular consequence of the t(8;14) and its variants is deregulation of the *MYC* oncogene in 8q24 through juxtaposition next to one of the *IG* enhancer elements in the *IGH* (14q32), *IGK* (2p12), or *IGL* (22q11) locus. Activation of *MYC* takes place on the der(14) in t(8;14) and on the der(8) in t(2;8) and t(8;22). Correspondingly, the breakpoints on the der(8) differ between the t(8;14) and its variants being telomeric of the *MYC* gene in the latter and centromeric of *MYC* in the former. Breakpoints can scatter over several hundred kilobases on both sides of the *MYC* locus (Joos et al., 1992a, 1992b; Einerson et al., 2006; Kroenlein et al., 2012). Sporadic, endemic, and immunodeficiencyassociated BL show different clustering of the breakpoints on der(14) and der(8), indicating that different pathogenetic mechanisms may be behind the generation of the t(8;14) in these different disease settings. Briefly, the breakpoints of t(8;14) in endemic BL frequently fall far centromeric of the *MYC* gene and regularly affect the J-segments of the *IGH* locus. In contrast, t(8;14) in sporadic BL more frequently involves the switch regions of the constant segments of *IGH*, or the breakpoint occurs between exons 1 and 2 or immediately 5′ of the *MYC* gene. This molecular heterogeneity has to be taken into account when diagnosing one of the translocations by molecular or molecular cytogenetic techniques, and therefore, it is advisable always to use both a *MYC* break-apart and *MYC–IGH* fusion FISH assay as far

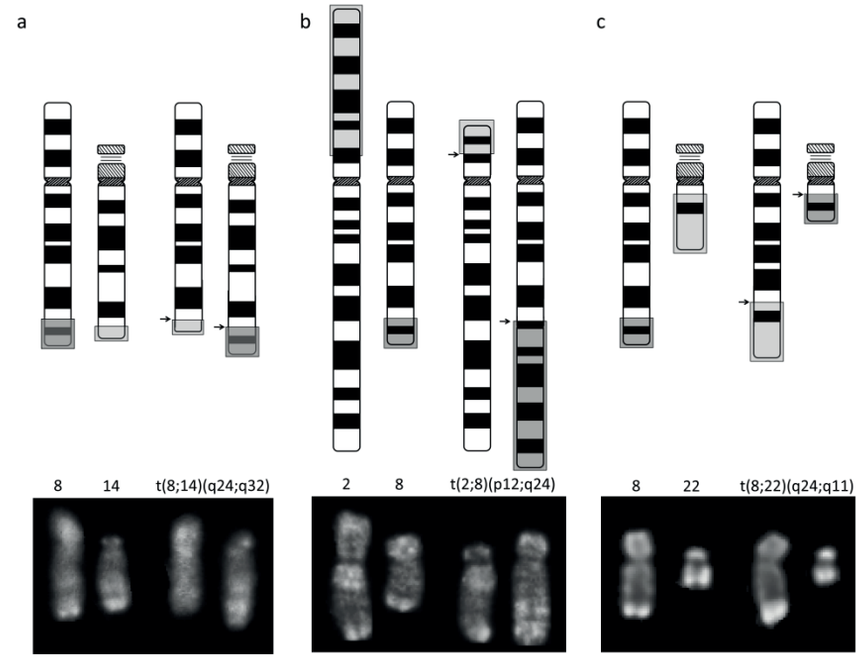

Figure 2.3 | Burkitt translocation t(8;14) and variants. (A) Ideogram and partial karyotype with t(8;14)(q24;q32) involving MYC and IGH. (B) Ideogram and partial karyotype with t(2;8)(p12;q24) involving IGK and MYC. (C) Ideogram and partial karyotype with t(8;22)(q24;q11) involving MYC and IGL. Fluorescence R-banding.

centromeric breakpoints may be missed using a break-apart assay alone (Hummel et al. 2006). In addition, somatic mutation of the *MYC* locus occurs frequently in BL, which might in part be driven by the VH mutation machinery after the juxtaposition of *MYC* next to *IGH*. Some of the mutations in *MYC*, which may also occur independently of *IGH*-driven hypermutation, might be of pathogenetic relevance. For more details on the molecular characteristics of the Burkitt translocations as well as the pathogenic consequences of *MYC* activation in general, the reader is referred to excellent reviews by, for example, Willis and Dyer (2000), Boxer and Dang (2001), Küppers and Dalla-Favera (2001), Küppers (2005), Klapproth and Wirth (2010), and Ott et al. (2013).

Typically in BL, the t(8;14) or variant translocation is part of a rather simple karyotype; complex karyotypes indicate disease progression and are an adverse prog-

nostic factor (Johansson et al., 1995; Hummel et al., 2006; Salaverria et al., 2008; Boerma et al., 2009; Poirel et al., 2009). Secondary chromosomal changes are present in around 60% of BL (Berger et al., 1989; Johansson et al., 1995; Boerma et al., 2009) In a comparison of paired karyotypes from BL patients, complex karyotypes were seen at a higher frequency in relapsed or progressive BL compared to initial diagnostic samples (Aukema and Siebert, in prep.); this may contribute to the very dismal prognosis of patients with progressing and relapsing disease (Woessmann, 2013). The clearly most frequent secondary aberration (>30% of all patients) is structural rearrangement of chromosome 1, in particular of the long arm and often leading to partial trisomy for 1q. Trisomy 7 and trisomy 12 are other common secondary changes. These three aberrations tend to be mutually exclusive in BL progression (Boerma et al., 2009). Another hot spot for secondary involvement in BL is chromosomal region 13q3, found rearranged in 15% (Johansson et al., 1995). The target is most likely the *miR-17-92* miRNA locus that, like other recurrent molecular changes, seems to interact with *MYC* in transformation (He et al., 2005; O'Donnell et al., 2005). Losses of 13q may be associated with a more unfavorable outcome (Nelson et al., 2010). In addition to secondary chromosomal changes, whole-genome and wholeexome sequencing studies have identified recurrent mutations in *MYC*, *TP53*, *ID3*, *TCF3*, *CCND3*, and *DDX3X* as common, with mutations targeting *ID3* or *TCF3* occurring in about 70% of sporadic BL cases (Campo, 2012; Love et al., 2012; Richter et al., 2012; Schmitz et al., 2012).

Although the putative existence of BLs lacking a *MYC* translocation has been subject of much discussion (Leucci et al., 2008), it is unlikely that "true" *MYC* translocation-negative BL exist. Recently, in a subset of lymphomas resembling BL by gene expression profile and pathological characteristics but importantly lacking *MYC* translocation, 11q aberrations with proximal gains and telomeric losses were identified (Salaverria et al., 2014).

The view that BL is a homogeneous disease characterized by the presence of one of the three specific translocations is also supported by gene expression profiling studies (Dave et al., 2006; Hummel et al., 2006). Nevertheless, none of the three translocations is completely specific for BL as all of them have been described also in several other B-cell lymphomas. "B-cell lymphoma with features intermediate between DLBCL and BL" is a disease subset strongly enriched for the presence of these translocations and might even present with a typical Burkitt leukemia morphology in the bone marrow (Kluin et al., 2008). In contrast to BL, these intermediate lymphomas, which occur at a significantly older age,

mostly show complex karyotypes (Hummel et al., 2006; Boerma et al., 2009; Salaverria and Siebert, 2011; Aukema et al., 2014). Many of them harbor other recurrent *IG* translocations such as t(14;18)(q21;q32) or t(3q27) targeting the *BCL6* locus. These so-called "doublehit" lymphomas are associated with a much more unfavorable outcome, highlighting the clinical relevance of distinguishing both subtypes (Dave et al., 2006; Hummel et al., 2006; Aukema et al., 2011). Moreover, a wide range of t(8q24) that do not involve *IG* loci as partners, such as t(8;9)(q24;p13) juxtaposing *MYC* to *PAX5* and t(3;8)(q27;q24) juxtaposing *MYC* to *BCL6* (Hummel et al., 2006; Bertrand et al., 2007; Sonoki et al., 2007), may also occur. The detection of a double hit, the presence of a non-*IG–MYC* translocation, and the occurrence of a t(8;14) or variant as part of a complex karyotype should, particularly in nonpediatric patients, lead to a reassessment of the histopathologic diagnosis, especially since each of these three features is associated with an unfavorable outcome (Hummel et al., 2006, Boerma et al., 2009; Aukema et al., 2011, 2014; Salaverria and Siebert, 2011). In cases where a diagnosis of BL is in doubt, profiling for BL-specific genes (the analysis can also be performed on formalin-fixed and paraffin-embedded tissues) as well as mutational analysis (e.g., for *ID3* and *TCF3* mutations that are absent in other *MYC* translocation-positive lymphomas) may be helpful in establishing the correct diagnosis (Love et al., 2012; Richter et al., 2012; Schmitz et al., 2012; Masque-Soler et al., 2013).

Clinical correlations

The cytogenetic changes in mature lymphoid neoplasms and their clinical impact greatly depend on the disease subtype in which they occur. They have therefore mostly been discussed in the respective disease-specific sections.

The most important clinical reason for identifying chromosomal aberrations in suspected mature lymphoid neoplasms is the fact that they provide essential information on which a correct, precise diagnosis can be based. Different histopathologic subtypes of mature lymphoid neoplasms are associated with very different natural courses and show quite different responses to therapy. Modern therapy for mature lymphoid neoplasms relies on the proper classification of the lymphoma, and the patterns of both primary and secondary chromosomal aberrations constitute part of the foundation for that classification. Indeed, comments on the 2001 WHO classification recommend that cytogenetic analysis be performed in all cases and should form part of the pathology report (Harris et al., 1999, 2000).

It has to be emphasized that the same chromosomal aberrations may have different prognostic impact in the various subtypes of mature lymphoid neoplasms. Among NHL, for example, t(11;14) (q13;q32) mostly signifies a MCL that has a poor prognosis, although a subgroup of MCL with this translocation and favorable prognosis exists (Navarro et al., 2012). In contrast, t(11;14) in MM defines a disease subset with a relatively favorable outcome (though compared to t(11;14)-positive MCL, the overall survival of patients with t(11;14)- positive MM is still worse). Moreover, t(11;14) can be detected in preneoplastic disorders like MGUS and in quite indolent diseases like SLVL. These findings point to the need to integrate cytogenetic analysis into an interdisciplinary diagnostic workup of mature lymphoid neoplasms, which, besides histopathologic features and the immunophenotype, also takes into account both the clinical presentation and the neoplastic cells' genetic characteristics. It can be anticipated that the diagnostic process will soon also see the integration of findings made by array-based technologies like gene expression profiling as well as high-throughput sequencing.

Despite the fact that the clinical relevance of cytogenetic changes in mature lymphoid neoplasms always has to be evaluated in the context of the disease subtype, a few common themes generally associated with unfavorable outcome seem to exist: in most instances of mature lymphoid neoplasms, the rule of thumb is that the more complex the karyotype, the worse is the prognosis. A notable exception here is cHL that is characterized by highly complex karyotypes, and yet long-term cure rates far exceeding 80% are reached with modern therapy. Losses of 17p and 9p are supposed to mostly target the *TP53* and *TP16* gene loci. One or both changes are associated with unfavorable outcome in many mature lymphoid neoplasms, including CLL, FL, MCL, and DLBCL. Finally, translocations affecting the band 8q24 mostly target the *MYC* oncogene. In most types of mature lymphoid neoplasms, including FL, MCL, and DLBCL, these changes are associated with increased clinical aggressiveness and an unfavorable prognosis. The notable exception here is BL in which t(8;14) and variants are the pathognomonic alterations. Despite being a biologically highly aggressive disease, BL can be cured in most instances, particularly in children.

The near future will see the increasing introduction of molecular cytogenetic techniques like FISH and array CGH into the diagnosis of mature lymphoid neoplasms. Indeed, interphase FISH is already widely used for the diagnosis of the most recurrent alterations in CLL and MM and is also becoming a routine tool for the detection of diagnostically relevant chromosomal alterations in formalin-fixed, paraffin-embedded tissues (Ventura et al., 2006). Nevertheless, in contrast to chromosome banding analysis, interphase FISH will never provide a full overview of all chromosomal aberrations of a mature lymphoid neoplasm. This carries the very real risk that clinically relevant alterations, like t(8q24) in t(14;18)-positive FL, might be missed simply because they were not searched for. Moreover, a subclone with prognostically unfavorable chromosomal aberrations may be missed by FISH, whereas it might be detected by conventional cytogenetics due to a proliferative advantage of these cells. Finally, complex and variant FISH patterns might be difficult to interpret without knowledge of the metaphase chromosomal picture, the karyotype.

The advent of array CGH and related techniques enables the production of a wealth of new data at a resolution somewhere between the cytogenetic and molecular levels. One should exercise considerable caution when trying to translate findings and conclusions between the microscopic cytogenetic and the array-based information realms. As can be seen from the previous discussion of 13q deletions in MM, the diagnostic impact of a chromosomal change may seemingly depend on the technique with which it was detected (Dewald et al., 2005). Both small and large genetic changes can be missed if one exclusively relies on only one technique, not least if the change in question is present only in a subclone. The results are invariably best if different techniques and investigative principles are allowed to complement each other.

Recent technological developments have allowed high-throughput sequencing to become a part of both scientific and diagnostic analyses of lymphatic neoplasms. These new techniques provide valuable information helping us to understand the pathogenesis of neoplastic diseases better as well as to make more meaningful diagnoses and choose the optimal treatment. Prominent examples are *ID3* mutations in BL, *MYD88* mutations in Waldenström disease, or *RHOA* mutations in ATLL. In principle, sequencing technologies are able to detect all kinds of genomic alterations, be they balanced translocations, imbalances, or mutations. In practice, this may not be so easy, not least when it comes to translocations with repeat-rich breakpoints. In addition, the subclonal composition of tumors is hard to evaluate if these techniques are used alone. Finally, a wealth of bioinformatic challenges need to be resolved for daily use. It nevertheless seems beyond doubt that the future will see an integration of the different tumor genetic techniques also for diagnostic purposes, in lymphatic neoplasms

as elsewhere, with important clinical benefits for the patients (Biesecker et al., 2012; Yates and Campbell, 2012; Mwenifumbo and Marra, 2013).

It should finally be stressed that the treatment of many mature lymphoid neoplasms is now undergoing profound changes. Probably, the most important recent improvement in the treatment of the most common lymphomas, including the mature B-cell lymphomas MCL, FL, and DLCBL, was the introduction of anti-CD20 immunotherapy (Rituxan) (Coiffier et al, 2002; Kluin-Nelemans et al., 2012). Almost all cytogenetic studies referred to earlier were performed before the introduction of this therapy, and we do not know whether the cytogenetic–prognostic correlations detected during the pre-Rituxan era still apply when the new antibody treatment is given. Indeed, with the exception of CLL and MM and in part BL and DLBCL, hardly any systematic cytogenetic studies within clinical trials exist. This needs to be changed in future so that cytogenetic studies as well as molecular studies form an essential and integral part of prospective clinical trials; only then can the clinical impact of the various acquired genomic changes in mature lymphoid neoplasms be reliably assessed.

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